BALANCING FORMULATION AND DEVICE INTEGRATION: INSIGHTS INTO CHALLENGES AND ALTERNATIVES IN HIGH-CONCENTRATION SUBCUTANEOUS DRUG DEVELOPMENT

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INTRODUCTION

Background

The growing demand for subcutaneous (SC) drug administration, especially for high-dose indications, has driven the development of high-concentration formulations.[1] While chemical issues like deamidation and isomerization are typically independent of drug delivery, physical challenges such as aggregation, viscosity, and volume are closely tied to device selection. High-concentration formulations also face reduced yields due to potential equipment adsorption and blockages, further linking formulation and device teams in SC combination product development. High-concentration, small-volume formulations have historically been pursued with hopes of reaching a volume that is appropriate for autoinjectors (<3 mL). However, with newer device advancements such as large-volume on-body delivery systems (OBDSs) (e.g., enFuse®), formulation teams can now consider low-concentration, large-volume formulations, which allow teams to circumvent the management of physical formulation challenges. This survey is a continuation of a review article published by the authors[1] on low-concentration, large-volume formulations. This survey study explores the preferences and challenges faced by formulation science experts in the development of high-concentration formulations and gauges whether low-concentration, large-volume formulations could be preferred during SC drug development.

Objectives: To understand perspectives, challenges, preferences, and downstream effects on device integration associated with the development of high-concentration SC drug products and explore the potential benefits and trade-offs of using OBDSs with large volume capacities (5-25 mL) in reducing formulation complexity, associated risks, and expediting development timelines and costs.

METHODS

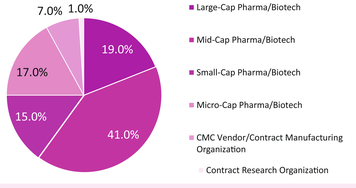
A blinded survey garnered 100 responses from formulation and chemistry, manufacturing, and controls (CMC) experts with experience in creating high-concentration liquid formulations for SC delivery. The survey included multiple-choice and open-ended questions to capture current practices, challenges, and expert opinions on SC formulation development.

RESULTS

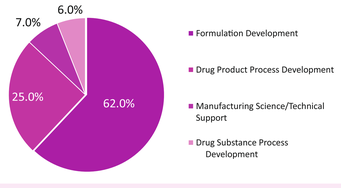
Professional Background and High-Concentration Formulation Experience

- A total of 100 CMC/formulation science experts completed the survey; most worked in formulation development in large- or mid-cap pharma/biotech.
- Most (53%) were in the US, with remaining participants in Europe (37%) or Asia (10%).
- Participants **had a mean of 13.44 (SD 7.13) years of experience** working on **a mean of 19.12 (SD 56.12) SC high-concentration biologics.** Most biologics (58.0%) were monoclonal antibodies.
- On a scale of 1 (Not Familiar) to 5 (Very Familiar), participants rated their familiarity with creating high-concentration SC formulations at a mean of 4.49 (SD 0.67).

Type of Organization



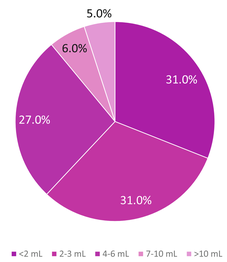
Primary Area of Specialization



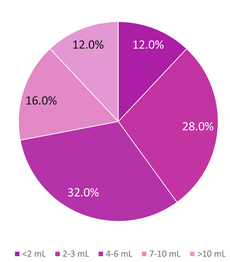
High-Concentration Formulation Development Challenges and Risks

- The **most challenging aspects of high-concentration SC biologic development include issues with solubility, viscosity, and aggregation; pharmacology and/or clinical planning; and additional manufacturing costs**.
- These challenges, especially difficulties with aggregation, viscosity, and solubility, **delay entry into clinical trials and delay launch, most commonly for 3-15 months.**
- **Stability was the most common barrier to commercial use,** while **drug substance availability and processing, screening, and stability nearly equally contributed to delays in clinical trials.**

Perceived Maximum Drug Volume That Can Be Administered SC as a Bolus Without a Permeation Enhancer

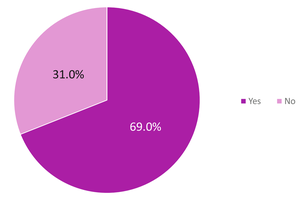


Perceived Maximum Drug Volume That Can Be Administered Over Several Minutes Without a Permeation Enhancer

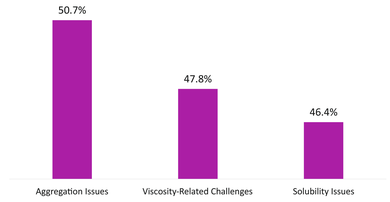


Most participants attributed beliefs about the maximum drug volume that can be administered SC without a permeation enhancer either as a bolus or over several minutes to familiarity with commercialized SC drugs or peer-reviewed literature.

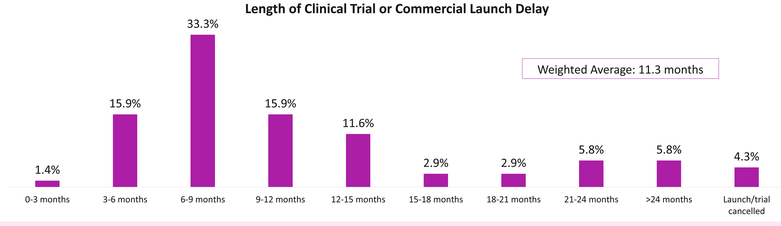
Have Challenges in the Process of Creating a High-Concentration SC Biologic Ever Delayed Entry of a Product into Clinical Trials or Delayed the Launch of a Product?



Top 3 Challenges Contributing to the Delay in Entry of High-Concentration SC Biologic into Clinical Trials or Launch



Length of Clinical Trial or Commercial Launch Delay



High-Concentration Formulation Development Preferences

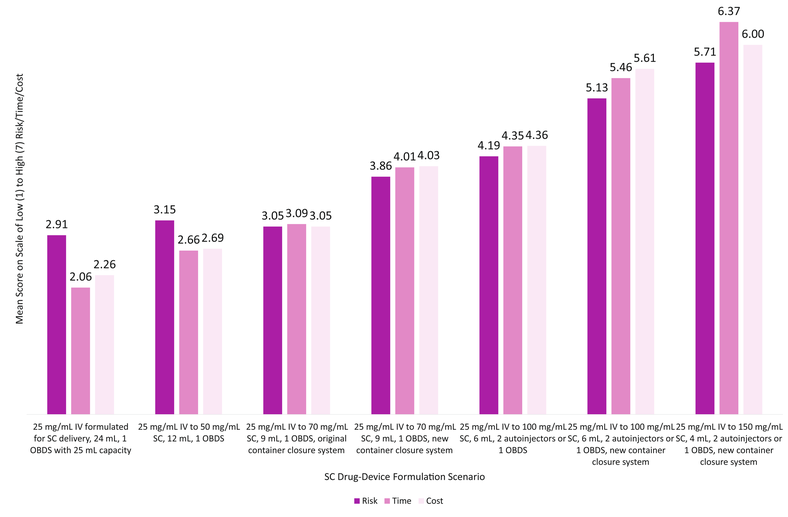
On a scale of 1 (Strongly Disagree) to 5 (Strongly Agree), most participants agreed or strongly agreed that **using traditional excipients and protein drug concentrations combined with a large-volume delivery device like an OBDS is**

- **less risky** (mean 4.15, median 4, mode 4),
- **quicker** (mean 3.95, median 4, mode 4), and
- **more cost-effective** (mean 4.27, median 4, mode 4)

than the process of developing a high-concentration liquid formulation (≥100 mg/mL) for use with a conventional small-volume autoinjector.

Specifically, as shown in the figure below, approaches to transitioning a formulation from IV delivery to SC delivery that involved **up-concentrating the formulation to reduce the injection volume and/or changing the primary container were rated as riskier, more time-consuming, and more costly than maintaining the concentration of the formulation and using a large-volume delivery device like an OBDS**.

Risk, Time, and Cost of Approaches to Transitioning from IV Delivery of a 25 mg/mL IV Antibody Drug to SC Delivery of a 600 mg Antibody Drug



CONCLUSIONS

These findings suggest that low-concentration, large-volume SC formulations could be advantageous from a time, cost, and risk perspective. OBDSs that support large volume capacity (5-25 mL) such as enFuse® may reduce formulation complexity and risks and increase yield, potentially expediting development and reducing costs. This strategic approach could mitigate some of the challenges faced in high-concentration formulation development and improve market readiness.

[1]Desai et al. Monoclonal antibody and protein therapeutic formulations for subcutaneous delivery: high-concentration, low-volume vs. low-concentration, high-volume. *mAbs.* 2023;15(1):2285277.

If you have questions about this poster, please email Omar Rahman at orahman@enableinjections.com.
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